Cystic fibrosis in the young and old: The future is precision medicine

Jeffrey B. Hoag, M.D. and Vincent Chan, M.D.

ABSTRACT

Background: *Cystic fibrosis (CF) is an autosomal recessive genetic disorder that leads to impairment in function of the CF transmembrane conductance regulator (CFTR), a chloride channel that normally resides in the apical membranes of exocrine gland cells. Dysfunction of these channels leads to broad phenotypes characterized by increased thickness of secretions in the aero-respiratory, hepatobiliary, pancreatic, gastrointestinal, and reproductive organ systems among others. Since its first description as a clinical entity with pathologic cystic changes and fibrosis of the pancreas, CF has been associated with shortened life expectancy, with progressive respiratory infections and failure as the most common cause of death.*

Methods: *Literature review was performed using relevant search terms to identify articles for inclusion in this brief review focusing on diagnosis, available treatments, and future potential targets of precision medicine.*

Results: *Fortunately, there has been a tremendous collaborative effort among people with CF (pwCF), their families, care providers, and the scientific community to develop therapies to relieve symptoms, treat infections and inflammation, and improve nutrition, which results in a robust improvement in longevity of pwCF. Since the discovery and sequencing of the CFTR gene in 1989, treatment focus has shifted to develop therapeutics that restore function of mutated channels and, thus, treat the underlying cause of CF.*

Conclusion: *This article provides a brief review of the clinical symptoms of CF, diagnostic strategies, currently approved treatments, and future targets of precision medicine to restore CFTR function.*

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Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by impaired function of the CF transmembrane conductance regulator (*CFTR*), a chloride channel that resides in apical membranes of exocrine glands and other tissues. Alteration in *CFTR* function leads to thickened secretions in the sinopulmonary, gastrointestinal, and other organ systems, thus impairing normal function. Since the first description as a clinical entity,[1] CF has been known to cause bronchiectasis with airway obstruction and respiratory infections, pancreatic insufficiency with associated malnutrition, fat-soluble vitamin deficiencies, and fertility issues among many other ailments. Respiratory symptoms commonly include productive cough with dyspnea on exertion and airflow obstruction on pulmonary function testing with reduced forced expiratory volume in 1 second (FEV_1)/forced vital capacity. The severity of lung disease is characterized by the degree of obstruction (FEV_1) and frequency of pulmonary exacerbations, both of which are markers of worse outcomes.[2] Chronic bacterial colonization of the respiratory secretions often starts with *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant) and *Haemophilus influenzae* in childhood, but, over time, frequency of colonization with more fastidious and problematic Gram-negative bacteria such as *Pseudomonas aeruginosa* predominate. With the latter, there is also an association with more-rapid lung function decline and increased risk for death.[2,3] In addition to pulmonary manifestations of CF, liver effects can include transaminitis, biliary obstruction with progression to cirrhosis complicated by portal hypertension, and varices once advanced. Malabsorption of fats due to pancreatic insufficiency and associated fat-soluble vitamin deficiency in a large proportion of people with CF (pwCF) (up to 90%) (2023 Cystic Fibrosis

From the Division of Pulmonary, Critical Care and Allergy; Department of Medicine, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania
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Address correspondence to Jeffrey B. Hoag, M.D., Sidney Kimmel Medical College, Thomas Jefferson University, 15 S. 12th Street; c/o 1101 Chestnut Street, Honickman Center 17th Floor, Philadelphia, PA 19107

E-mail address: Jeffrey.hoag@jefferson.edu
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Foundation [CFF] 2023 Registry[4]). Many other manifestations of CF can occur because of the disease, which are outside of the scope of this review. Herein, we provide a brief review of the clinical symptoms, diagnostic approach, currently treatments, and future targets of precision medicine to restore *CFTR* function.

METHODS

A literature review was performed through PubMed and Google Scholar (Google. 1600 Amphitheatre Parkway, Mountain View, CA) to provide support for this article with search terms that included "cystic fibrosis," "cystic fibrosis transmembrane conductance regulator," "sweat chloride testing," "cystic fibrosis genetics," "modulator therapies," "precision medicine," "gene therapies," and "cystic fibrosis metabolic syndrome." Search terms were used alone and in combination to identify relevant articles for review. Treatment guidelines were also identified through review of the CFF website.[5] Clinical trial information was accessed through website.[6] Because the results of this search strategy were immense, articles were limited to those defined as CFF "guidelines," those cited in "guidelines," or those published within the past 7 years.

DIAGNOSIS

CF remains a clinical diagnosis, although there are well-established guidelines and algorithms designed to provide structure to diagnostic approach and provide clarity in the setting of sometimes uncertain presentations.[7] After 2010, newborn screening for CF has been adopted in all states in the United States; however, there is considerable variability in the specifics of newborn testing across the country.[8] In the 2023 iteration of the CFF's annual registry report,[4] ~60% of all patients included in the registry were diagnosed through newborn screening; thus, approximately one third of pwCF presented to clinicians with symptoms and other findings, inciting clinical suspicion to move toward more-definitive testing. Along with having signs and symptoms consistent with CF, functional testing (sweat chloride, nasal potential difference, or intestinal current measurement), demonstrating abnormal *CFTR* function helps confirm the diagnosis. Hundreds of years before the initial descriptions of CF as a clinical entity, children who tasted salty to the kiss were thought to be bewitched and would die early.[7] Capitalizing on the knowledge of abnormal chloride concentration in the sweat of individuals with CF has been the bedrock of clinical testing to diagnose this disorder.[7,10] Sweat chloride testing is susceptible to erroneous results, and proper performance of the testing is paramount to accurate results. Standards have been developed to ensure that the appropriate volume of sweat collected, two samples from different locations or days, timing of testing after obtaining sweat samples, and adherence to Clinical and Laboratory Standards Institute guidelines.[7] In the setting of clinical or family history or positive newborn screening, systematic testing of sweat chloride through approved laboratories defines *CFTR* dysfunction (Fig. 1). Cutoffs of chloride concentrations between 30 and 59 mmol/L define the indeterminate range that requires additional evaluation, whereas individuals with values ≤ 29 mmol/L make CF unlikely and those individuals with values ≥60 mmol/L confirm the diagnosis of CF. As with all testing, there are causes of false positives and negatives that need to be excluded. When patients have intermediate results, additional functional testing and genetic testing should be performed to help support or refute the diagnosis.[7]

In conjunction with functional testing, the genetics of CF are one of the most well characterized and described of all autosomal recessive disorders. After the gene was initially sequenced in 1989,[11–13] there have been >2000 mutations in *CFTR* identified, although most are quite rare and many do not lead to alterations in *CFTR* function. By far the most common mutation in *CFTR* is F508del with a prevalence of ~44% of individuals with CF as homozygous and an additional 41% of individuals heterozygous for variants in the US CFF Registry.[4] The remaining ~15% of variants are much less common, although, as of 2023, 718 additional variants have been identified in individuals with clinical CF.[14]

Mutations in *CFTR* are grouped into categories based on similar characteristics of alterations in the chloride channel caused by the mutations. The most detrimental class includes nonsense mutations that lead to complete absence of *CFTR* protein. Others mutations, such as F508del, cause abnormal posttranslational folding, preventing trafficking of *CFTR* to the apical cell surface. Others may lead to problems with channel regulation, decreased conductance, decreased synthesis, or decreased stability.[15] The latter four examples are often referred to as partial function mutations because they preserve some ability to conduct chloride, albeit with only a fraction of that of normal, nonmutated *CFTR*. An understanding of the genetic effects of each mutation and its relative *CFTR* effects serves as the basis of newer therapeutics and targets of precision therapies that will be discussed later.

CURRENTLY AVAILABLE TREATMENTS

Treatments for CF have followed our understanding of the pathogenesis of the disease through time, with initial options for therapy that focuses on replacement of pancreatic enzymes, followed by use of antibiotics

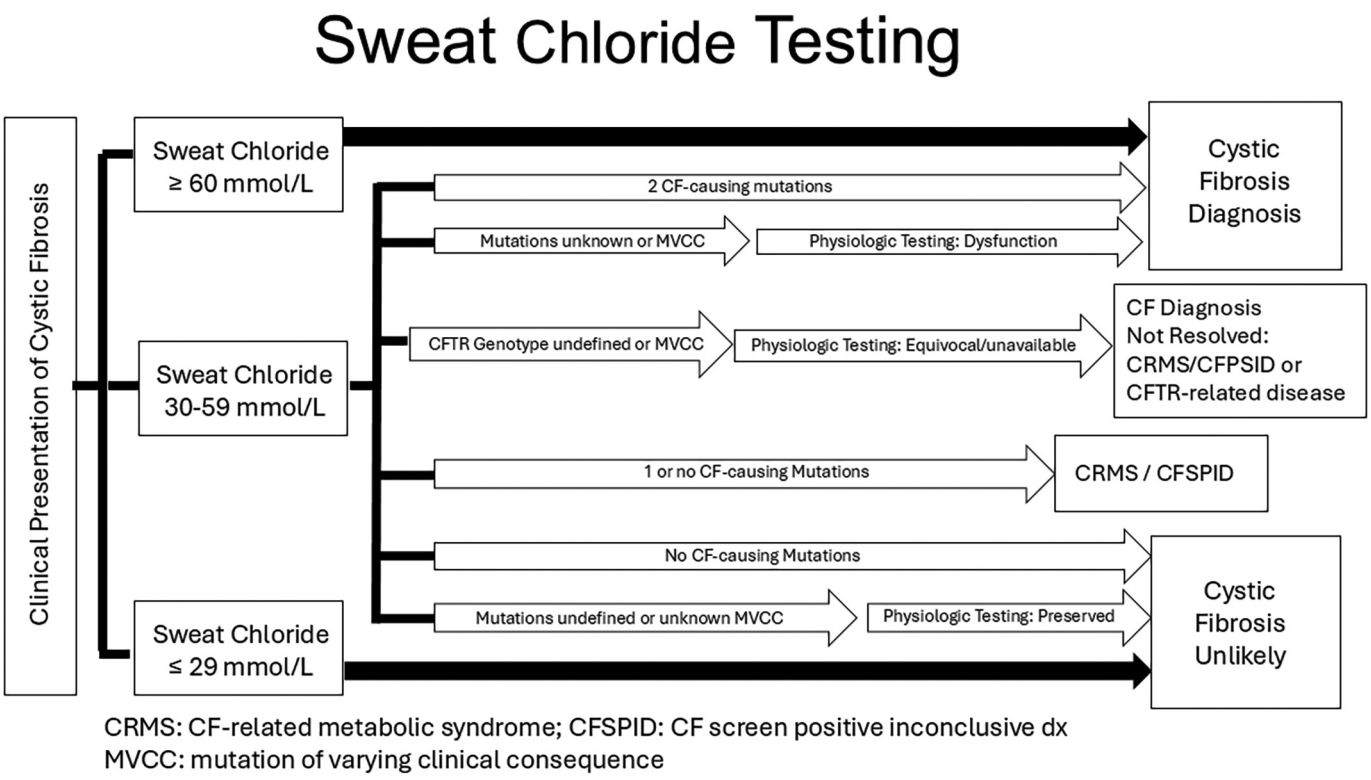
Sweat Chloride Testing
Clinical Presentation of Cystic Fibrosis
Sweat Chloride ≥ 60 mmol/L
Sweat Chloride 30-59 mmol/L
Sweat Chloride ≤ 29 mmol/L
2 CF-causing mutations
Mutations unknown or MVCC
Physiologic Testing: Dysfunction
Cystic Fibrosis Diagnosis
CFTR Genotype undefined or MVCC
Physiologic Testing: Equivocal/unavailable
CF Diagnosis Not Resolved: CRMS/CFPSID or CFTR-related disease
1 or no CF-causing Mutations
CRMS / CFSPID
No CF-causing Mutations
Mutations undefined or unknown MVCC
Physiologic Testing: Preserved
Cystic Fibrosis Unlikely
CRMS: CF-related metabolic syndrome; CFSPID: CF screen positive inconclusive dx
MVCC: mutation of varying clinical consequence

Figure 1. *CF is diagnosed when an individual has both a clinical presentation of the disease and evidence of CFTR dysfunction. The tests of CFTR function are not always done in this order, but hierarchically to establish the diagnosis of CF, sweat chloride should be considered first, then CFTR genetic analysis, and then CFTR physiologic tests. All individuals diagnosed with CF should have a sweat test and a CFTR genetic analysis performed. Rare individuals with a sweat chloride <30 mmol/L may be considered to have CF if alternatives are excluded and the other confirmatory tests (genetic, physiologic testing) support CF. If only 1 CFTR variant is identified on limited analysis, further ("extended") CFTR testing should be performed. CF is possible if both alleles possess CF-causing, undefined, or mutation of varying clinical consequence (MVCC) mutations; CF is unlikely if only non-CF-causing mutations are found. If a CF diagnosis is not resolved, CRMS/CFSPID (following NBS) or CFTRrelated disorder should be considered. Rarely, no distinct label may be appropriate but further follow-up may be warranted. In these cases, the use of "CF carrier" or the specific clinical problem should be used for characterization/labeling purposes. Sweet chloride testing. CRMS = Cystic fibrosis transmembrane conductance regulator–related metabolic syndrome; CFSPID = cystic fibrosis screen positive inconclusive diagnosis; MVCC = mutation of varying clinical consequence. Adapted from Ref 7.*

for frequent and recurrent infections, and then with medications designed to mitigate the thickened respiratory secretions in the airways. As with many diseases, treatment regimens began through anecdote until a clearer understanding of pathogenesis was determined and allowed for disease-specific therapies to be developed. One of the first systematic guidelines for therapy for pwCF was developed by providers and families of those with CF assembled into the early CF care center network, which would later morph into the current-day CFF.[16,17] Originally described as pillars of care, recommendations included nutritional repletion, relief of airway obstruction, treatment of airway infection, and suppression of inflammation. Through extensive clinical trial execution, partnership with CF care providers, pwCF, and the CFF guidelines have been developed for most aspects of CF disease, including chronic medications for lung health,[18] airway clearance therapies,[19] management of nutrition,[20] management of liver disease,[21] management of CF-related diabetes,[22] mental health screening,[23] and models of post-transplantation care,[24] among many others accessible through the CFF's guidelines website.[25] Although these foundational treatment recommendations remain paramount to current management, they all suffer from the same flaw; *viz.*, they target sequelae of the disease and do not alter the primary pathogenesis of the chloride channel dysfunction.[25]

MODULATOR THERAPIES

Since identification and sequencing of *CFTR*,[11–13] many astute clinicians and scientists have understood that the future of therapies will be aimed at restoring abnormal *CFTR* function through myriad techniques that capitalize on the knowledge of how each mutation

alters production, trafficking, and function of the chloride channel. The first such medications developed to restore *CFTR* function are globally referred to as "modulators" that function through correcting, potentiating, stabilizing, and amplifying the abnormal *CFTR* channel function based on the specific genetic mutations, and the past decade has been truly a remarkable time for precision medicine in CF. The first such medication, ivacaftor, is described as a potentiator due to its action of increasing the probability that *CFTR* will be open and conduct chloride more effectively and was initially developed for patients with a specific class 3 gating mutation (*G551D*).[26] This pivotal trial, published in 2011, demonstrated a very robust improvement in FEV_1 (10%), with a significant decrease in exacerbations, increase in weight, and improvement in quality of life, which led to rapid U.S. Food and Drug Administration (FDA) approval of this medication in 2012. Most importantly, this trial demonstrated a decrease in sweat chloride, from 100 mmol/L to 50 mmol/L, demonstrating efficacy through correcting the underlying defect in chloride conductance through *CFTR*. Subsequently, additional mutations with similar gating characteristics were found to respond effectively, thus increasing access to an additional subset of patients with CF. Unfortunately, those with *F508del*, the most common mutation in pwCF, did not fare well with this medication. Mechanistically, this makes sense because *F508del* is a trafficking mutation, which leads to a misfolded, destabilized *CFTR* that is often degraded before movement into its normal location of action. Additional high-throughput screening of small molecules identified candidates that improved *CFTR* stability in those with F508del mutations and additional combination medications were FDA approved in 2015 (lumacaftor/ivacaftor) and 2018 (tezacaftor/ivacaftor). Although effective, these medications did not have the same robust improvement in lung function, weight, and exacerbations compared with ivacaftor in patients with the appropriate genotype; although, these medications are recommended by the CFF guidelines[27] for use in appropriate patients. The next landmark trial in CF modulators was completed in 2019 with a triple combination termed ETI (elexacaftor, tezacaftor, ivacaftor).[28] ETI improved FEV_1 by 14%, the largest improvement in FEV_1 in any CF trial, while decreasing exacerbation frequency to 25% of placebo and improving body mass index and quality of life significantly in pwCF, with at least one copy of F508del.[28] Again, this medication exerts its action through improving chloride conductance through *CFTR* and decreasing sweat chloride by 45 mmol/L within the trial. ETI was FDA approved in 2019 just before the pandemic and has been a revolutionary therapy for a huge percentage of pwCF, increasing accessibility of precision medications to ~90% of pwCF.[4] Additional clinical trials are underway for next generation modulators, with hopes of increasing access to people not currently eligible by genotype or people with tolerability issues to current modulators. One such example is the recent phase III Skyline Clinical Trials that evaluated "Vanza" Triple (VX-121/tezacaftor/deutivacaftor), a once-daily three-drug *CFTR* modulator therapy (NCT05033080).[6]

With the increase in access to modulator therapies in addition to sequelae-specific medications, life expectancy has moved rapidly to >60 years of age for those born with CF in this decade.[4] Severe respiratory exacerbation frequency and lung transplantation frequency has decreased to ~25%, and pregnancy frequency has more than doubled compared with pre-ETI annual rates.[4] Although the development and widespread access to modulator therapy is truly remarkable and life changing for pwCF, there remains between 10 and 20% of pwCF who are not currently on modulator therapy and rely solely on previous treatment strategies due to inaccessible mutations, medication intolerance,[4] or cost. Unfortunately, this group of people ineligible for modulator-therapy are disproportionately represented by people of color who do not carry F508del.

PRECISION MEDICINE AND FUTURE THERAPEUTICS IN CF

Unfortunately, almost 10% of pwCF who do not have access to disease-modifying therapies currently because of specific genotypes and up to another 10% are not on modulators due to medication intolerability, toxicities, or cost-related issues, thus highlighting the need for additional precision treatments. Moreover, those with mutations inaccessible to modulators are disproportionately represented by people of color who do not have *F508del*. In addition, nonsense mutations (class 1) have incomplete transcription due to the presence of early stop codons or a canonical splice-site mutation. In these cases, there is a need to deliver an entirely new DNA or RNA for *CFTR* to incorporate a functional channel. This creates a particularly difficult problem due to many factors, including the size of the *CFTR*,[29] delivery into specific cells that lack *CFTR*, and the need to remain stable for the life of the person with CF. DNA delivery methods include adeno-associated virus and lentiviruses transfection. In addition, to avoid immunogenic issues with viral vectors, alternative options for RNA delivery can use lipid nanoparticles to provide an entire *CFTR* messenger RNA (mRNA) for the host cell to translate into viable, stable protein.[29]

Some splice-site mutations are located in exons, whereas others reside in intron regions that highlight the need for mutation agnostic genetic treatment approaches. Recent research advances capitalize on the use of superexons; fully derived exon mRNA sequences available for translation.[30] This allows for bypass of

premature stop codons. Secondarily, antisense oligonucleotides, designed to bind to specific mRNA sites, allow for the bypass of mutated exons.[31] Circumventing early stop codons results in the production of modified proteins, which would otherwise have been abnormal or absent. A third mechanism, by using CRISPR (clustered regularly interspaced short palindromic repeats) has been shown to be useful in precise genetic editing by being able to substitute genes with a newly desired gene.[32] This requires the use of a guide RNA to correctly identify the sequence motif near the target site and recruit CRISPR-associated protein 9 to cut the DNA, leaving a resultant double-stranded break. This then actives the cell's natural repair mechanism, which allows for homologous recombination with the desired gene to be inserted, resulting in the introduction of a gene into the sequence. These technologies allow for insertion of wild-type CF genes in those with previously rare mutations or nonsense mutations to offer a pathway for universal treatment of any person with any *CFTR* mutation. These studies are highlighted in the CFF Drug Development Pipeline.[33]

CFTR-RELATED DISEASE

Some individuals with a single *CFTR* mutation experience a spectrum of clinical findings termed *CFTR*-related metabolic syndrome. Clinically, most individuals with *CFTR*-related metabolic syndrome are healthy, although ~10% may experience symptoms of sinus or pulmonary disease and may have positive sputum cultures with bacteria similar to those with overt CF such as *P. aeruginosa*.[34] Testing demonstrates normal or indeterminate sweat chloride without two CF-causing mutations and only some characteristics related to *CFTR* abnormality. This group may also benefit with precision therapies once a greater understanding of relative effects on one mutation or partial function are identified. There are currently recommendations for surveillance of these people without specific robust treatment options.[34]

CONCLUSION

In the new era of CF treatment, knowledge of specific gene mutations is ripe for development of precision targets for therapy. Over the past decade, there has been an explosion of life-altering treatment options for many pwCF, and the horizon is bright for a time when all pwCF with any mutation will have mutation agnostic therapeutic options to restore *CFTR* function and restore normal quality of life and longevity.

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